dissolution of the drug following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants surprisingly discovered that nanoparticulate compositions could effectively be formulated into controlled release formulations. This is not shown or suggested by the cited prior art.

II. THE OFFICE ACTION

Claims 1-35 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,718,919 to Ruddy et al. Office Action at page 2. Applicants respectfully traverse this ground for rejection.

A. Examiner's Basis for the Rejection of the Claims over Ruddy et al.

In support of the rejection, the Examiner stated that while Ruddy et al. do not teach the specifically claimed controlled release formulation, the reference teaches that the described composition "can be formulated into any form well known in the pharmaceutical art . . . [and] it is the position of the examiner that the specific concentrations, and forms of the composition are limitations that would be routinely determined by one of ordinary skill in the art . . ." Office Action at page 2. In addition, the Examiner stated that Ruddy et al.'s teaching of the use of the polymer HPMC as a surface stabilizer in the described composition obviates the claimed invention, which is directed to the use of a rate-controlling polymer in a nanoparticulate composition. Office Action at page 3. Applicants courteously disagree with the Examiner's analysis and conclusion.

B. Ruddy et al. Do not Teach or Suggest a Controlled Release Nanoparticulate Composition

Ruddy et al. describe a nanoparticulate composition of the R(-) enantiomer of ibuprofen or fenoprofen. This patent is limited to a pharmaceutical composition of ibuprofen or fenoprofen having immediate and sustained release properties. The immediate release is a result of the formulation design. However, the sustained release is

dependent upon the pharmacokinetic properties of ibuprofen or fenoprofen; the sustained release properties do not result from the design of the formulation.

Ibuprofen exists in two chiral forms: the R(-) and the S(+) forms. When the R(-) form is administered, it readily and extensive converts to the S(+) form in humans. *See* col. 1, lines 31-34, of Ruddy et al. This is significant in that as a result of the bioconversion, the effective elimination half-life of the S(+) enantiomer is up to 50% greater than that following the administration of the S(+) form alone, thereby producing sustained release. *See* col. 1, lines 34-37, of Ruddy et al. However, administration of the S(+) form exhibits a much faster onset of action than the R(-) form of ibuprofen. *See* col. 1, lines 39-43, of Ruddy et al.

Prior Art Problem Described by Ruddy et al.:

Administration of R(-) ---bioconversion---→ S(+) = sustained release, but slow onset of action

Administration of S(+) ----------→ = fast onset of action, but short period of pharmacological response

The problem presented by the art prior to Ruddy et al. was how to combine the sustained release of the R(-) enantiomer with the rapid onset of action exhibited by the S(+) enantiomer.

Ruddy et al. solved the prior art problem by making a R(-) ibuprofen formulation having a fast onset of activity. This does not teach or suggest the claimed invention.

1. Ruddy et al. Contrasts the Claimed Compositions with a Controlled Release Formulation

Ruddy et al. specifically contrast the described dosage form with a controlled release dosage form, stating that while this combination of immediate release and sustained release "might be achieved using some kind of controlled release system, such systems involve additional cost and complexity." *See* col. 2, lines 43-45, of Ruddy et al. Thus, Ruddy et al. do not teach or suggest a controlled release nanoparticulate

composition. In fact, this reference teaches **away** from Applicants' claimed controlled release compositions and methods of making and using such compositions.

2. The Claimed Formulations of Ruddy et al. Are Characterized by a Fast On-set of Activity

The invention of Ruddy et al. solves the problem of the prior art ibuprofen compositions by combining the prolonged effect resulting from administration of the R(-) enantiomer with a fast-onset formulation of the R(-) enantiomer. The fast-onset R(-) enantiomer results from the nanoparticulate size of the R(-) ibuprofen particles, which produce rapid dissolution upon administration. *See* col. 2, lines 35-45, of Ruddy et al.

Thus, the goal of the invention of Ruddy et al. was to develop a formulation of the R(-) ibuprofen enantiomer having fast onset of action; it was **not** to develop a controlled release formulation of the compound.

Because Ruddy et al. do not teach or suggest the claimed invention, withdrawal of the rejection of the claims is respectfully requested.

III. CONCLUSION

Applicants courteously request reconsideration of this application in view of the above remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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